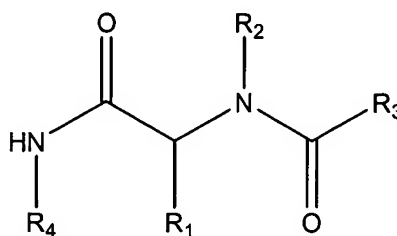


## CLAIMS

What is claimed is:

1. A method of inhibiting rejection of a transplanted organ, tissue or cell in a mammal, the method comprising the step of administering to the recipient  
5 mammal an effective amount of an immunosuppressive agent and an effective amount of a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

10 R<sub>1</sub> is a substituted or unsubstituted aryl group or a substituted or unsubstituted alkyl group;

R<sub>2</sub> is an optionally substituted aralkyl group or an alkyl group substituted with -NR<sub>5</sub>R<sub>6</sub>;

R<sub>3</sub> is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

15 R<sub>4</sub> a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

R<sub>5</sub> and R<sub>6</sub> are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R<sub>5</sub> and R<sub>6</sub> taken together with the nitrogen to which they are attached are a non-aromatic  
20 heterocyclic group.

2. The method of Claim 1 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.
3. The method of Claim 1 wherein the mammal is the recipient of a transplanted stem cell(s).
- 5 4. The method of Claim 1 wherein the transplanted organ, tissue or cell is xenogenic or bio-engineered.
5. The method of Claim 1 wherein the immunosuppressive agent is an anti lymphocyte antibody.
6. The method of Claim 1 wherein the immunosuppressive agent is an anti-CD40L  
10 monoclonal antibody or rapamycin.
7. The method of Claim 1 wherein  $R_2$  is an optionally substituted heteroaralkyl group or an alkyl group substituted with  $-NR_5R_6$ .
8. The method of Claim 7 wherein:  
15 a)  $R_1$  is an optionally substituted aryl group or an optionally substituted  $C_1$ - $C_4$  aralkyl group;  
b)  $R_3$  is an optionally substituted aryl group or an optionally substituted  $C_1$ - $C_4$  aralkyl group; and  
c)  $R_4$  is an optionally substituted aryl group, an optionally substituted  
20 cycloalkyl group, an optionally substituted  $C_1$ - $C_4$  aralkyl group or an optionally substituted  $C_1$ - $C_4$  cycloalkylalkyl group.

9. The method of Claim 7 wherein:

- a)  $R_1$  is an optionally substituted phenyl group or an optionally substituted phenyl- $C_1$ - $C_4$  alkyl group;
- b)  $R_3$  a substituted or unsubstituted phenyl, phenyl- $C_1$ - $C_4$ -alkyl, diphenyl- $C_1$ - $C_4$ -alkyl, pyrazolyl, pyrazolyl- $C_1$ - $C_4$ -alkyl, indolyl, indolyl- $C_1$ - $C_4$ -alkyl, thienylphenyl, thienylphenyl- $C_1$ - $C_4$ -alkyl, furanylphenyl, furanylphenyl- $C_1$ - $C_4$ -alkyl, fluorenyl, fluorenyl- $C_1$ - $C_4$ -alkyl, naphthyl, naphthyl- $C_1$ - $C_4$ -alkyl, quinoxaliny, quinoxaliny- $C_1$ - $C_4$ -alkyl, an optionally substituted quinazolinyl, an optionally substituted quinazolinyl- $C_1$ - $C_4$ -alkyl, pyrrolyl, pyrrolyl- $C_1$ - $C_4$ -alkyl, thienyl, thienyl- $C_1$ - $C_4$ -alkyl, furanyl or furanyl- $C_1$ - $C_4$ -alkyl; and
- c)  $R_4$  is an optionally substituted phenyl group, an optionally substituted phenyl- $C_1$ - $C_4$ -alkyl group, an optionally substituted diphenyl- $C_1$ - $C_4$ -alkyl group, an optionally substituted  $C_3$ - $C_8$ -cycloalkyl- $C_1$ - $C_4$ -alkyl group or an optionally substituted di- $(C_3$ - $C_8$ -cycloalkyl)- $C_1$ - $C_4$ -alkyl group.

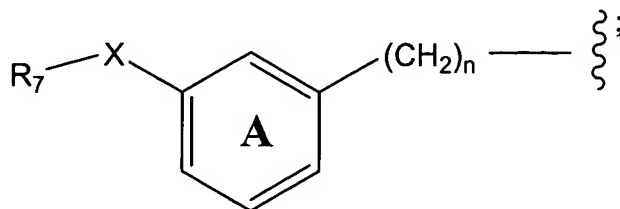
10. The method of Claim 9 wherein  $R_2$  is an optionally substituted imadazolyl- $C_1$ - $C_4$ -alkyl group or a  $C_1$ - $C_4$  alkyl group substituted with  $-NR_5R_6$ .

11. The method of Claim 10 wherein:

- $R_1$  is a phenyl group or phenyl- $C_1$ - $C_4$  alkyl group each optionally substituted with R,  $-CH_2R$ ,  $-OCH_2R$ ,  $-CH_2OC(O)R$ ,  $-OH$ , halogen,  $-OR$ ,  $-O-COR$ ,  $-COR$ ,  $-CN$ ,  $-NO_2$ ,  $-COOH$ ,  $-SO_3H$ ,  $-NH_2$ ,  $-NHR$ ,  $-N(R)_2$ ,  $-COOR$ ,  $-CHO$ ,  $-CONH_2$ ,  $-CONHR$ ,  $-CON(R)_2$ ,  $-NHCOR$ ,  $-NRCOR$ ,  $-NHCONH_2$ ,  $-NHCONRH$ ,  $-NHCON(R)_2$ ,  $-NRCONH_2$ ,  $-NRCONRH$ ,  $-NRCON(R)_2$ ,  $-C(=NH)-NH_2$ ,  $-C(=NH)-NHR$ ,  $-C(=NH)-N(R)_2$ ,  $-C(=NR)-NH_2$ ,  $-C(=NR)-NHR$ ,  $-C(=NR)-N(R)_2$ ,  $-NH-C(=NH)-NH_2$ ,  $-NH-C(=NH)-NHR$ ,  $-NH-C(=NH)-N(R)_2$ ,

-NH-C(=NR)-NH<sub>2</sub>, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)<sub>2</sub>,  
 -NRH-C(=NH)-NH<sub>2</sub>, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)<sub>2</sub>,  
 -NR-C(=NR)-NH<sub>2</sub>, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>,  
 -SO<sub>2</sub>NHR, -SO<sub>2</sub>N(R)<sub>2</sub>, -SH or -SokR;

5 R<sub>3</sub> is represented by the following structural formula:



R<sub>4</sub> is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with -OH, halogen, R, -CH<sub>2</sub>R, -OCH<sub>2</sub>R, -CH<sub>2</sub>OC(O)R, -OR,  
 10 -O-COR, -COR, -CN, -NO<sub>2</sub>, -COOH, -SO<sub>3</sub>H, -NH<sub>2</sub>, -NHR, -N(R)<sub>2</sub>, -COOR,  
 -CHO, -CONH<sub>2</sub>, -CONHR, -CON(R)<sub>2</sub>, -NHCOR, -NRCOR, -NHCONH<sub>2</sub>,  
 -NHCONRH, -NHCON(R)<sub>2</sub>, -NRCONH<sub>2</sub>, -NRCONRH, -NRCON(R)<sub>2</sub>,  
 -C(=NH)-NH<sub>2</sub>, -C(=NH)-NHR, -C(=NH)-N(R)<sub>2</sub>, -C(=NR)-NH<sub>2</sub>, -C(=NR)-NHR,  
 -C(=NR)-N(R)<sub>2</sub>, -NH-C(=NH)-NH<sub>2</sub>, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)<sub>2</sub>,  
 15 -NH-C(=NR)-NH<sub>2</sub>, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)<sub>2</sub>,  
 -NRH-C(=NH)-NH<sub>2</sub>, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)<sub>2</sub>,  
 -NR-C(=NR)-NH<sub>2</sub>, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>,  
 -SO<sub>2</sub>NHR, -SO<sub>2</sub>N(R)<sub>2</sub>, -SH or -SO<sub>k</sub>R;

20 Ring A substituted or unsubstituted; R<sub>7</sub> is an optionally substituted phenyl, furanyl, thienyl or pyridyl group; n is an integer from 1-4; and X is a bond, CH<sub>2</sub>, OCH<sub>2</sub>, CH<sub>2</sub>OC(O), CO, OC(O), C(O)O, O, S, SO or SO<sub>2</sub>;

each R is independently C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl,

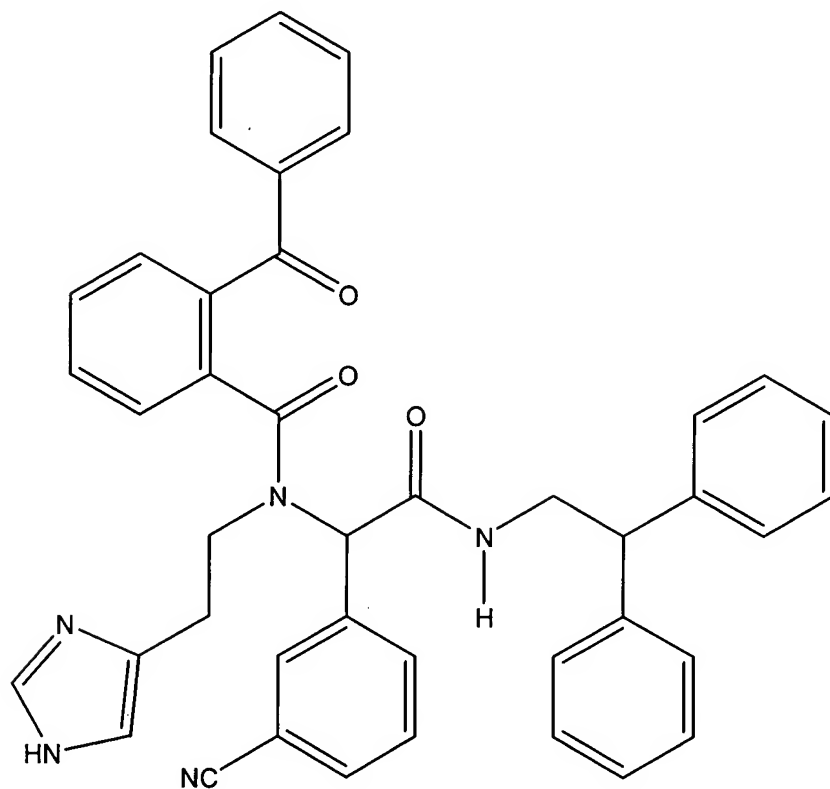
alkylaminocarbonyl, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl; and

k is zero, one or two.

12. The method of Claim 11 wherein R<sub>1</sub> is a phenyl group or phenyl-C<sub>1</sub>-C<sub>2</sub> alkyl group, each optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, CN, C<sub>1</sub>-C<sub>4</sub>-alkylthiol, C<sub>1</sub>-C<sub>4</sub>-haloalkyl or phenoxy; R<sub>4</sub> is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, CN, C<sub>1</sub>-C<sub>4</sub>-alkylthiol, C<sub>1</sub>-C<sub>4</sub>-haloalkyl or phenoxy; R<sub>7</sub> is an optionally substituted phenyl group; n is 1; and X is CO.
13. The method of Claim 12 wherein Ring A is unsubstituted and R<sub>7</sub> is a phenyl group optionally substituted with R, -CH<sub>2</sub>R, -OCH<sub>2</sub>R, -CH<sub>2</sub>OC(O)R, -OH, halogen, -OR, -O-COR, -COR, -CN, -NO<sub>2</sub>, -COOH, -SO<sub>3</sub>H, -NH<sub>2</sub>, -NHR, -N(R)<sub>2</sub>, -COOR, -CHO, -CONH<sub>2</sub>, -CONHR, -CON(R)<sub>2</sub>, -NHCOR, -NRCOR, -NHCONH<sub>2</sub>, -NHCONRH, -NHCON(R)<sub>2</sub>, -NRCONH<sub>2</sub>, -NRCONRH, -NRCON(R)<sub>2</sub>, -C(=NH)-NH<sub>2</sub>, -C(=NH)-NHR, -C(=NH)-N(R)<sub>2</sub>, -C(=NR)-NH<sub>2</sub>, -C(=NR)-NHR, -C(=NR)-N(R)<sub>2</sub>, -NH-C(=NH)-NH<sub>2</sub>, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)<sub>2</sub>, -NH-C(=NR)-NH<sub>2</sub>, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)<sub>2</sub>, -NRH-C(=NH)-NH<sub>2</sub>, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)<sub>2</sub>, -NR-C(=NR)-NH<sub>2</sub>, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR, -SO<sub>2</sub>N(R)<sub>2</sub>, -SH or -SO<sub>k</sub>R.
14. The method of Claim 13 wherein R<sub>7</sub> is a phenyl group; and R<sub>2</sub> is 2-(imidazol-4-yl)ethyl.

15. A method of inhibiting rejection of a transplanted organ, tissue or cell in a mammal, the method comprising the step of administering to the recipient mammal an effective amount of an anti CD40L monoclonal antibody or rapamycin and an effective amount of a compound represented by the following structural formula:

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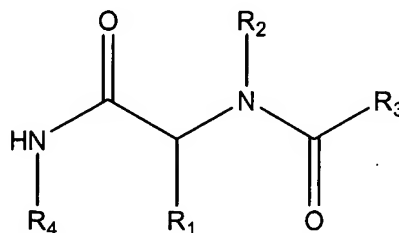


or a pharmaceutically acceptable salt of the compound.

16. The method of Claim 15 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.

17. A composition comprising an immunosuppressive agent and a compound represented by the following structural formula:

5



or a physiological salt thereof, wherein:

$R_1$  is a substituted or unsubstituted aryl group or a substituted or unsubstituted alkyl group;

10  $R_2$  is an optionally substituted aralkyl group or an alkyl group substituted with  $-NR_5R_6$ ;

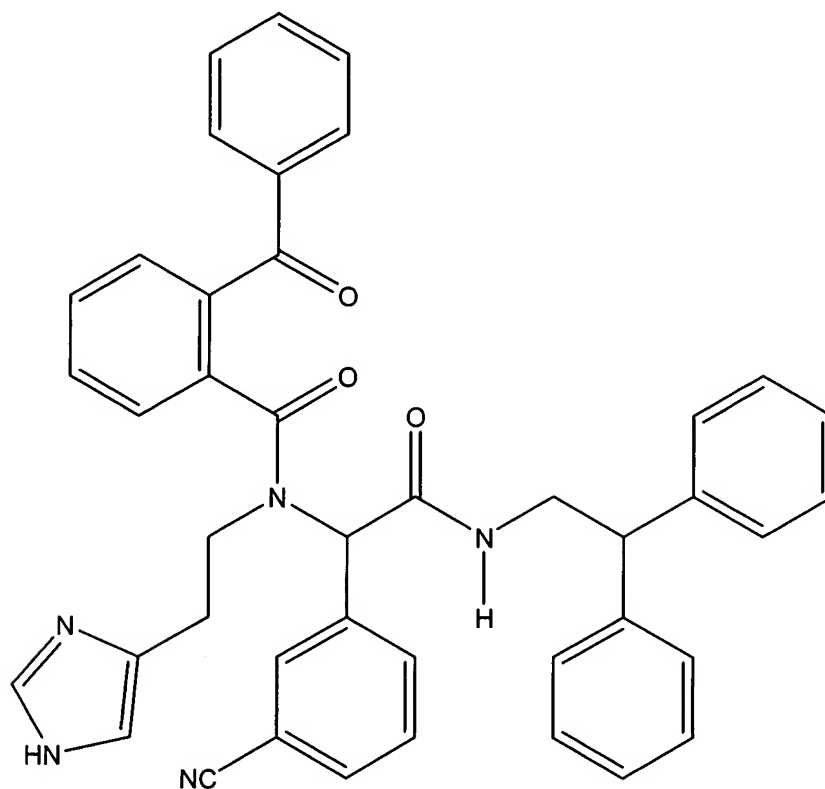
$R_3$  is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

$R_4$  a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

15  $R_5$  and  $R_6$  are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or  $R_5$  and  $R_6$  taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group.

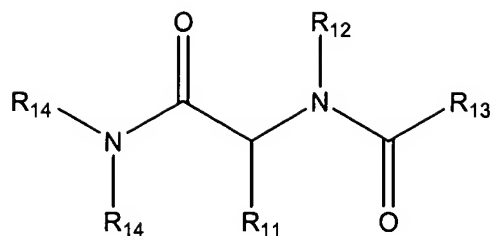
18. The composition of Claim 17 wherein the immunosuppressive agent is an anti  
20 CD40L monoclonal antibody or repamycin.

19. A composition comprising an anti CD40L monoclonal antibody or repamycin and a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.





$R_{11}$  is -H, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heteroaralkyl;

5  $R_{12}$  is alkyl substituted with  $NR_{15}R_{16}$ , a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaralkyl, or a substituted or unsubstituted heterocycloalkylalkyl;

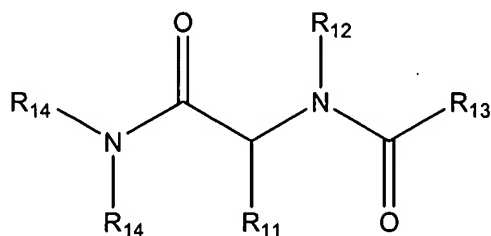
$R_{13}$  is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted benzophenonyl, or a substituted or unsubstituted cycloalkylalkyl; and

15 each  $R_{14}$  is independently, -H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heteroaralkyl;

$R_{15}$  and  $R_{16}$  are independently selected from H, a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl or unsubstituted aralkyl or  $R_{15}$  and  $R_{16}$  together with the nitrogen to which they are attached are a heterocycloalkyl.

20 20. A method of inhibiting rejection of a transplanted organ, tissue or cell in a mammal, the method comprising the step of administering to the recipient

mammal an effective amount of an immunosuppressive agent and an effective amount of a compound represented by the following structural formula:



5  $\text{R}_{11}$  is -H, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heteroaralkyl;

$\text{R}_{12}$  is alkyl substituted with  $\text{NR}_{15}\text{R}_{16}$ , a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaralkyl, or a substituted or unsubstituted heterocycloalkylalkyl;

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$\text{R}_{13}$  is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted benzophenonyl, or a substituted or unsubstituted cycloalkylalkyl; and

15

each  $\text{R}_{14}$  is independently, -H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heteroaralkyl;

$\text{R}_{15}$  and  $\text{R}_{16}$  are independently selected from H, a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl or unsubstituted aralkyl or  $\text{R}_{15}$  and  $\text{R}_{16}$  together with the nitrogen to which they are attached are a heterocycloalkyl.

20